

# Acute viral hepatitis with bridging necrosis. Collaborative study on chronic hepatitis

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ABSTRACT - Bridging necrosis was recorded in 14% of 361 patients with acute viral hepatitis on examination of the liver biopsy. The clinical and biochemical features of acute viral hepatitis with bridging necrosis were compared with acute viral hepatitis with no bridging necrosis (NBN). It was noted that fever of more than 8 days' duration in the pre-icteric phase, the presence of mild ascites and pedal edema during the icteric phase, increasing or persistently high levels of serum bilirubin even 4 weeks after the onset of the icteric phase and positive hepatitis-B surface antigen were significantly more common in acute viral hepatitis with bridging necrosis. Hepatitis-B surface antigen clearance was slow in this group. The long-term complication of chronic hepatitis was more frequent in patients with acute viral hepatitis with bridging necrosis.

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In 1970, Boyer & Klatskin (1) focussed attention on the presence and the prognosis of bridging necrosis in acute viral hepatitis. Earlier, however, this condition had been described by Tisdale under the title of "Subacute hepatitis". In recent times this entity has been almost forgotten and, in fact, the International Association for the Study of the Liver has placed it in the column of "Rejected" nomenclature (2). The geographic pattern of liver disease may be quite variable; for example, non-cirrhotic portal fibrosis and extrahepatic portal hypertension are

much more common causes of variceal bleeding in India than cirrhosis of the liver, while in most European and other western countries the reverse is true (3).

A recent collaborative study carried out at three gastroenterology centers in our country concluded that chronic active hepatitis was a rare problem in India and that subacute hepatic failure and acute viral hepatitis with bridging necrosis were both far more frequently prevalent conditions throughout the country (4). The clinical, biochemical and pathological fea-

tures of subacute failure, which is associated with morphological changes of acute viral hepatitis with bridging necrosis, have recently been reported from our Centre (5).

The present paper describes: (a) the incidence of bridging necrosis in an unselected group of patients with acute viral hepatitis but without complications of acute or subacute liver failure; (b) the clinical and biochemical features which may help to detect the presence of bridging necrosis; and (c) the incidence of chronic hepatitis in these patients during 6–9 months follow-up.

## Material and methods

Liver biopsies of 361 patients with acute viral hepatitis, registered for a prospective national study on chronic hepatitis, were examined. Fifty patients were found to have bridging necrosis (AVH-BN) and the remaining 311 patients showed histopathological changes characteristic of acute viral hepatitis without bridging necrosis (AVH-NBN). The term "bridging necrosis" was applied when bands of necrosis involving one or more hepatic cell plates connected vascular territories of individual or adjacent lobules. These bands connect portal to portal territories, central (hepatic vein) to central territories or portal to central territories. Clinical, biochemical and morphological data were recorded on a precoded proforma in these two groups of patients, i.e. those with AVH-BN and AVH-NBN. All patients with AVH-BN and AVH-NBN were followed every week for 1 month and then every month for a further 5–8 months. Clinical data, liver function tests and HBsAg status were recorded during the follow-up period. Patients who still had any symptoms, signs or abnormalities of liver function tests after a minimum of 6 months in the follow-up period were subjected to liver biopsy. The statistical method employed was the chi-square test of independence. Widely accepted criteria for the diagnosis of chronic active (6), chronic persistent (6) and chronic lobular hepatitis (7) were used.

The diagnosis of chronic persistent hepatitis was established if, after recovery from the icteric stage and 6 months after acute hepatitis, liver biopsy (which was done due to persistence of some symptoms or palpable liver or persistent antigenemia or abnormal liver function tests) showed mild hepatic injury in the form of portal infiltrates predominantly comprising lymphocytes and intact lamina limitans. The clinical, biochemical and morphological profile of these pa-

tients with chronic persistent hepatitis is different from resolving viral hepatitis. The liver function tests were done using standard techniques. HBsAg was detected by the ELISA system (Auszyme, Abbott Lab, Chicago).

## Results

### Age, sex and associated factors

Table 1 compares the age and sex profiles of the two groups of patients (AVH-BN and AVH-NBN). The male-female ratio was approximately the same in both groups, i.e. 4:1. Thirty-two per cent of the patients with AVH-BN were above 50 years of age compared to 19% of the patients with AVH-NBN. The difference between the two is significant ( $P < 0.05$ ). A past history of viral hepatitis was obtained in 26% of the AVH-BN patients and in only 12% of those with AVH-NBN ( $P < 0.05$ ). Other factors like economic status, alcohol intake, contact with patients with hepatitis in the previous 6 months, a history of transfusion, surgical procedures or injection during the previous year and a history of intake of a known hepatotoxic drug during the previous 3 years did not differ in the two groups.

### Pre-icteric phase

In the pre-icteric phase, fever lasting 7 days or less was more common in patients with AVH-NBN (78%) than in those with AVH-BN (48%) ( $P < 0.001$ ). Fever lasting more than 8 days was seen in 52% of patients with AVH-BN but in

Table 1  
Age profile of patients with AVH-BN and AVH-NBN

	AVH-BN n=50 (%)	AVH-NBN n=311 (%)
12–29 years	17(34)	121(39)
30–49 years	17(34)	131(42)
50 years+	16(32)	59(19)*

\*  $P < 0.05$ .

only 22% of those with AVH-NBN ( $P < 0.01$ ). Other symptoms like jaundice, anorexia, a distaste for food, nausea, clay-coloured stools, vomiting, itching and fever was not different in the two groups ( $P > 0.05$ ). Similarly, no difference was noted in the mode of onset of illness, duration of the pre-icteric phase and degree of icterus in the two groups ( $P > 0.05$ ).

## Icteric phase

Pedal edema and ascites were uncommon features in either group. They were, however, more frequent in patients with bridging necrosis. Pedal edema was present in 23% and ascites in 16% of patients with AVH-BN. Their occurrence in patients without bridging necrosis was still less frequent, pedal edema being recorded in 9% and ascites in only 4% of these patients. The distribution of hepatomegaly and a palpable spleen was similar in the two groups ( $P > 0.05$ ).

## Liver function and hepatitis-B surface antigen status

Patients with bridging necrosis had sera positive for hepatitis-B surface antigen, twice as frequently (62%) as those without bridging necrosis (30%). Biochemical parameters of liver function, namely bilirubin, SGOT, SGPT, alkaline phosphatase and serum albumin did not show any significant difference between the two groups ( $P > 0.05$ ).

## Follow-up observations

During the follow-up period, clinical features and biochemical parameters of liver functions (transaminases, alkaline phosphatase and serum albumin) did not show any significant difference between the two groups. However, it was noted that hyperbilirubinemia (range 6–16 mg%) was more marked, occurring in 30% in AVH-BN at 4 weeks of the icteric phase as

Table 2

Comparison of antigen status in patients with AVH-BN and AVH-NBN on follow-up

Time	AVH-BN n = 50 (%)	AVH-NBN n = 311 (%)
At admission	31(62)	93(30)*
1st month	17(34)	18( 6)*
3rd month	8(16)	15( 5)**
6th month	6(12)	6( 2)**

\*  $P < 0.001$

\*\*  $P < 0.05$

compared with 10% of those with AVH-NBN ( $P < 0.001$ ).

The HBsAg clearance rate was slow in patients with AVH-BN. Their carrier rate was 6 times as high after 6 months as the carrier rate in patients with AVH-NBN (Table 2).

Table 3 shows that, at 6 months follow-up, 10% of the patients with bridging necrosis had developed chronic liver disease, 2% had chronic active hepatitis, 6% chronic persistent hepatitis and 2% chronic lobular hepatitis. Chronic liver disease was seen only in 2.6% of the patients without bridging necrosis; 1% had chronic active, 0.6% had chronic persistent and 1% had chronic lobular hepatitis.

## Liver biopsy (Fig. 1)

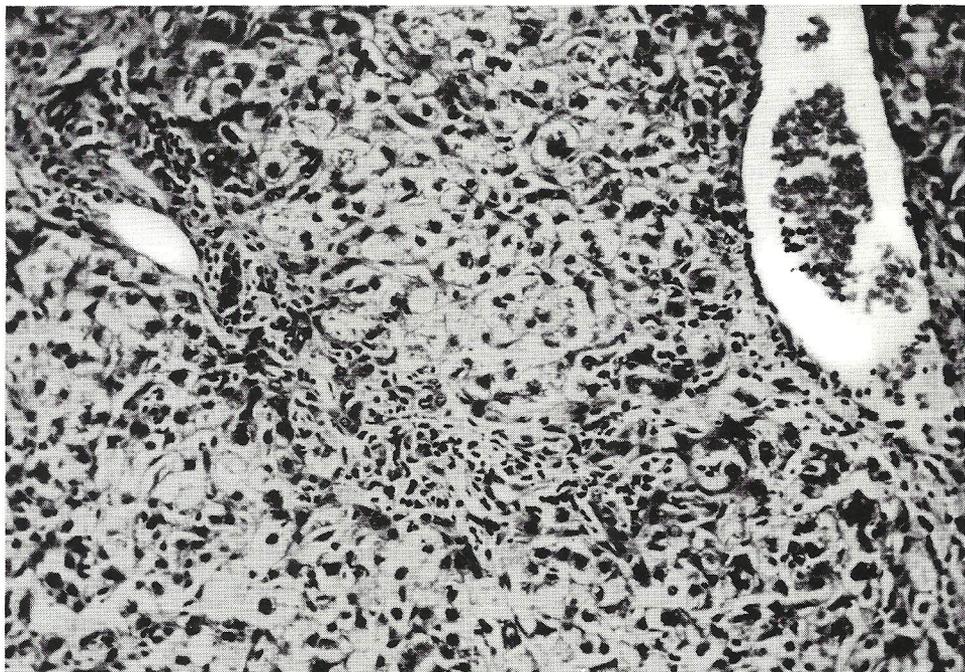
The liver biopsy size was adequate in all cases for the histopathological evaluation. Histo-

Table 3

Comparison of sequelae to chronic hepatitis in patients with AVH-BN and AVH-NBN at 6 months follow-up

Chronic hepatitis sub-group	AVH-BN n = 50 (%)	AVH-NBN n = 311 (%)
Chronic active hepatitis	1(2)	3(1)*
Chronic persistent hepatitis	3(6)	2(0.6)*
Chronic lobular hepatitis	1(2)	3(1)*

\*  $P < 0.05$



*Fig. 1.* Acute viral hepatitis with bridging. Broad band of bridge between portal tract and hepatic vein radical (H&E×300).

pathology of 50 cases of acute viral hepatitis with bridging necrosis showed that all the cases had narrow bridges, affecting liver parenchyma only one or two cell plates thick. Seventeen among the 50 showed broad bands of bridging necrosis involving more than two cell plates. Portal to portal bridging was seen in 47 biopsies, while portal to central and central to central bridging were seen in 31 and 20 biopsies, respectively. In 24 cases, multiple bridges were seen, although most of them were of the narrow type. Ballooning degeneration was mild in 17, moderate in 20 and severe in 13 cases. Polymorphonuclear leucocytic infiltration, predominantly in the areas of bridging necrosis, was seen in 48 cases. Lymphocytes were also observed in these areas and few plasma cells were seen in only 11 biopsies. Of the five patients from the bridging group who developed

chronic hepatitis, two had multiple bridging necrosis during the acute stage. The single case who ended up with the complication of chronic active hepatitis had multiple bridging necrosis during the acute stage.

## Discussion

The results of the present study suggest that bridging necrosis is present in 14% of unselected Indian patients with viral hepatitis without any clinical complications. Certain clinical and biochemical features, which will be discussed later, may be useful in indicating the presence of bridging necrosis in patients with acute viral hepatitis. Chronic hepatitis is a more frequent complication recorded in patients with acute viral hepatitis and bridging necrosis com-

pared to patients with acute viral hepatitis with no features of bridging necrosis in the liver biopsy. None of the patients with acute viral hepatitis with bridging necrosis in this prospective study developed the complication of subacute hepatic failure.

There are very few prospective studies into the incidence of acute viral hepatitis with bridging necrosis in the literature. In 1979, Nisman et al. (8), in a small series of 18 patients with acute viral hepatitis, reported the presence of bridging hepatic necrosis in five patients. These investigators realised the limitations of the very small size of their sample and suggested that studies with larger numbers and conducted in a similar manner might disclose the true incidence of bridging hepatic necrosis in acute viral hepatitis. Our study includes 361 unselected patients with acute viral hepatitis who reported to specialised clinics in three major centers of gastroenterology in this country, i.e. Madras, Cuttack, and Delhi. None of them presented with complications like acute liver failure or subacute hepatic failure. The prevalence of bridging hepatic necrosis in this group was 14%, which is much less than the 28% reported by Nisman et al. (8) in their series of 18 patients. In a retrospective study, Boyer & Klatskin (1) noted that bridging necrosis was present in 30% of the 170 patients of their study group admitted to hospital with acute viral hepatitis. Ware and coworkers (9), in a retrospective analysis, noted the presence of bridging necrosis in about one-third of patients with acute viral hepatitis who had a liver biopsy at their hospital over a 7-year period. Thus, a comparison with the results of both retrospective and prospective studies from a few centers in the USA shows that acute viral hepatitis with bridging necrosis is significantly less frequent in India. However, the incidence of 14% noted in our country is also quite high.

It was noted in the present study that bridging necrosis was significantly more common in patients with acute viral hepatitis who had the following characteristics: age above 50 years, a

past history of viral hepatitis, fever lasting more than 8 days in the pre-icteric phase, virus-B infection, and persistent or increasing bilirubin levels 4 weeks after the onset of jaundice. Sex, other presenting features like jaundice, anorexia, vomiting, distaste for food, cholestatic features and size of the liver enlargement were similar in the groups with or without bridging necrosis. Mild ascites and edema of the feet were frequently associated with bridging necrosis. Boyer & Klatskin (1) have reported that age above 40 years, ascites, edema and/or encephalopathy, 'a prothrombin time more than twice that of a control subject and a serum bilirubin of less than 3 g/DL increases the likelihood of bridging hepatic necrosis in acute viral hepatitis. Ware et al. (9), however, noted that two-thirds of their patients were less than 30 years of age; otherwise, their findings suggesting the possibility of bridging necrosis in acute viral hepatitis were similar to those reported by Boyer & Klatskin (1). Acute viral hepatitis with bridging necrosis was more frequent in females above the age of 40 years in a series reported by Tisdale (10), but this finding has not been confirmed and is different from the reports of all other investigators, who have not found any differences in the sex ratio for this disease (1, 8, 9).

Tisdale (10) suggested that a distinctive grieppe-like illness of 5-10 days duration in the pre-icteric phase of illness or vague symptoms for several weeks before the appearance of icterus should raise the possibility of AVH-BN. Boyer & Klatskin (1) noted that pre-icteric symptoms tended to be less severe in patients with AVH-BN. Results of the present study are more helpful and less vague in this respect. Continued fever lasting more than a week in the pre-icteric phase, which may even persist for a few days in the icteric phase, is suggestive of the possibility of AVH-BN. Jaundice was deeper and more prolonged in AVH-BN compared to AVH-NBN. The appearance of edemic feet and minimal ascites during this phase of illness has

been noted to be a most important pointer to AVH-BN by all investigators (1, 8, 9).

All the investigators (1, 8, 9) have emphasised virus-B as being the most important and frequent cause of acute viral hepatitis with bridging necrosis, which was also observed in the present series in 62% of the cases.

It has been suggested that acute viral hepatitis with bridging necrosis is associated with the frequent immediate complication of subacute hepatic failure characterized by ascites, edema and finally encephalopathy with a high mortality rate. All 50 patients with acute viral hepatitis and bridging necrosis were followed weekly for 1 month and monthly for 6-9 months. During this period, none of the patients developed subacute hepatic failure. There is no similar prospective study of AVH-BN reported in the literature. However, it is well established that liver biopsy of patients presenting with the clinical features of subacute hepatic failure almost always shows the presence of bridging necrosis and often similar liver histopathology is noted in patients with acute hepatic failure due to fulminant viral hepatitis. This has established AVH-BN as a bad prognostic finding, with the risk of serious complications like acute and subacute liver failure. Follow-up of large series of patients with AVH-BN will be necessary to determine the incidence of acute and subacute liver failure, associated with this liver pathology.

AVH-BN is reported to result in frequent long-term complications of chronic hepatitis and cirrhosis of the liver. Long-term follow-up lasting several years of patients with acute viral hepatitis to find out the incidence of cirrhosis of the liver is difficult. However, follow-up for 6 months is relatively easy and, therefore, it is possible to determine the incidence of chronic active hepatitis, chronic persistent hepatitis or chronic lobular hepatitis following an attack of acute viral hepatitis. These conditions were recorded in 2%, 6% and 2% of cases, respectively, leading to a total incidence of 10% of

chronic hepatitis at 6 months following an episode of acute viral hepatitis with bridging necrosis. The incidence of chronic hepatitis was only 2% in the group without bridging necrosis. Three of the five cases of AVH-BN who developed chronic hepatitis of one of the three types were HBsAg positive, while four of the eight with AVH-NBN were HBsAg positive. It seems that the development of chronic hepatitis in the present series was related more to the presence of bridging necrosis than to the positivity or negativity of HBsAg. Overall, it appears that multiple bridging necrosis compared to simple bridging from one vascular territory to another vascular territory does not particularly lead to chronic hepatitis, although in the present study the single case of chronic active hepatitis had multiple bridging necrosis.

Chung & Cha (11) have also reported from South Korea, a higher incidence of complications of chronic active and persistent hepatitis in a follow-up of a small number of similar patients. Their study, however, is not comparable with the present series due to different selection criteria for the patients in the initial period of registration.

It was also noted in the present series that patients with acute viral hepatitis with bridging necrosis had a higher hepatitis antigen carrier rate, compared to the group without bridging necrosis. This suggests the possibility of an increased risk of chronic liver disease related to persistent antigenemia in patients with acute viral hepatitis and bridging necrosis.

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